

Primary care

Efficacy of topical non-steroidal anti-inflammatory drugs in the treatment of osteoarthritis: meta-analysis of randomised controlled trials

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Abstract

Objective To assess the efficacy of topical non-steroidal anti-inflammatory drugs (NSAIDs) in the treatment of osteoarthritis.

Data sources Medline, Embase, Scientific Citation Index, CINAHL, Cochrane Library, and abstracts from conferences.

Review methods Inclusion criterion was randomised controlled trials comparing topical NSAIDs with placebo or oral NSAIDs in osteoarthritis. Effect size was calculated for pain, function, and stiffness. Rate ratio was calculated for dichotomous data such as clinical response rate and adverse event rate. Number needed to treat to obtain the clinical response was estimated. Quality of trial was assessed, and sensitivity analyses were undertaken.

Results Topical NSAIDs were more effective than placebo in relieving pain due to osteoarthritis only in the first two weeks of treatment. Effect sizes for weeks 1 and 2 were 0.41 (95% confidence interval, 0.16 to 0.66) and 0.40 (0.15 to 0.65), respectively. No benefit was observed over placebo in weeks 3 and 4. A similar pattern was observed for function, stiffness, and clinical response rate ratio and number needed to treat. Topical NSAIDs were less effective than oral NSAIDs in the first week of treatment and associated with more local side effects such as rash, itch, or burning (rate ratio 5.29, 1.14 to 24.51).

Conclusion Randomised controlled trials of short duration only (less than four weeks) have assessed the efficacy of topical NSAIDs in osteoarthritis. After two weeks there was no evidence of efficacy superior to placebo. No trial data support the long term use of topical NSAIDs in osteoarthritis.

Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) have been applied topically for decades. This route possibly reduces gastrointestinal adverse reactions by maximising local delivery and minimising systemic toxicity.¹ Some experimental evidence supports this, but bloodborne delivery may be the predominant mechanism for deep tissues at large joints.² Pain associated with osteoarthritis may be periarticular in origin rather than intracapsular, and topical applica-

tion may act through effects on peripheral and central sensitisation.³

Topical NSAIDs are popular with health professionals and with patients as over the counter medicines. Several randomised controlled trials of short duration (less than four weeks) have been undertaken in both periarticular lesions and osteoarthritis. A systematic review in 1998 confirmed that topical NSAIDs were superior to placebo over two weeks in the treatment of chronic pain, including pain due to osteoarthritis and tendinitis.⁴ We did a meta-analysis to determine the benefit of topical NSAIDs in treating osteoarthritis beyond two weeks.

Methods

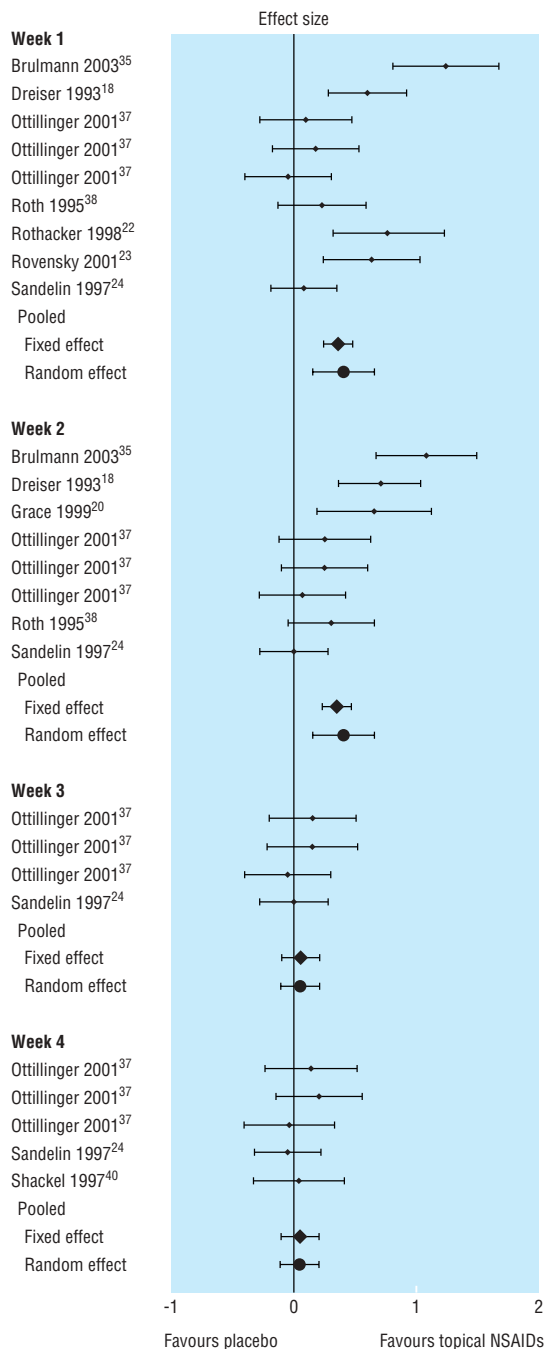
We identified reports of randomised controlled trials of topical NSAIDs compared with placebo or oral NSAIDs through a systematic search of the literature from 1966 to 31 October 2003 in Medline, Embase, CINAHL, the Scientific Citation Index and Cochrane Library. Titles and abstracts were reviewed and hard copies obtained for further scrutiny. Reference lists of original reports and review articles were searched, as were conference abstracts for 2002 and 2003 from international societies of rheumatology. See bmj.com for search terms.

Studies were selected if patients had clinical or radiographical evidence of osteoarthritis. Two rheumatologists cross checked and agreed on the diagnostic criteria in each trial. We excluded studies in conditions such as non-osteoarthritic joint pain; rheumatoid arthritis; pain due to dental extraction, surgery, or injury. Some studies included patients with either osteoarthritis or rheumatoid arthritis; we included them only if the subgroup data for osteoarthritis were available.

The quality of studies was assessed for randomisation, blinding, and withdrawal. Sensitivity analysis was used to assess the impact to the results of the quality components such as study design and withdrawal rate.⁵ Three of us extracted data independently using a customised form. Disagreements were resolved by discussion.



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Effect sizes (95% confidence intervals) in pain relief between topical non-steroidal anti-inflammatory drugs (NSAIDs) and placebo

The primary outcome measure was reduction in pain (global pain or pain at rest) from baseline. Other outcome measures included change in scores for function and stiffness. We assessed the clinical response rate, defined as the percentage of patients reporting at least moderate to excellent or greater than 50% pain relief or improvement in symptoms. Adverse events, expressed as the proportion of patients with any adverse events and the proportion of patients withdrawn due to adverse events, were analysed in total and by specific categories.

Statistical analysis

From individual studies we calculated the mean reduction and the standard deviation of the reduction from

the means and standard deviations of the scores for pain, function, and stiffness at baseline and end point. The standard mean difference or effect size was then calculated. The rate ratio was estimated for dichotomous outcomes such as the clinical response rate and adverse event rate. Number needed to treat to obtain clinical response was reported only if it was statistically significant, otherwise “not significant” was used to avoid confusion owing to its unique mathematical features. We statistically pooled the data. A random effects model was used for heterogeneous trials. Possible publication bias was sought by a funnel plot and Egger test.⁶

Results

We identified 133 citations. After exclusions, 13 trials totalling 1983 patients were included in the meta-analysis (see bmj.com). All trials, except for one with unknown sponsorship, were sponsored or partially sponsored by pharmaceutical companies. No details were given on method of randomisation. The withdrawal rate was 1% to 23%. A funnel plot showed noticeable asymmetry in the 11 placebo controlled trials (see bmj.com).

Topical NSAIDs were more effective than placebo in the first two weeks of treatment but not the following two weeks (figure and table 1). Topical NSAIDs were less effective than oral NSAIDs numerically at any week and statistically in the first week.

The effect size for improvement in function also showed superiority of topical NSAIDs over placebo in the first two weeks but not in weeks 3 and 4 (table 1). A

Table 1 Pooled effect sizes for pain relief and improvements in function and stiffness in randomised controlled trials comparing topical non-steroidal anti-inflammatory drugs (NSAIDs) with placebo or oral NSAIDs

Variable	No of trials	No of patients	Pooled effect size (95% CI)	χ^2 for heterogeneity
Topical NSAIDs versus placebo				
Pain:				
Week 1	7	1000	0.41 (0.16 to 0.66)*	35.49
Week 2	6	893	0.40 (0.15 to 0.65)*	27.48
Week 3	2	442	0.05 (-0.11 to 0.22)	1.02
Week 4	3	558	0.04 (-0.11 to 0.19)	1.68
Function:				
Week 1	4	566	0.37 (0.20 to 0.53)*	4.60
Week 2	4	540	0.35 (0.19 to 0.53)*	6.87
Week 3	1	208	0.10 (-0.18 to 0.38)	—
Week 4	1	208	0.26 (-0.02 to 0.54)	—
Stiffness:				
Week 1	1	74	0.64 (0.19 to 1.09)*	—
Week 2	1	81	0.33 (-0.13 to 0.79)	—
Week 3	NA	NA	NA	NA
Week 4	NA	NA	NA	NA
Topical NSAIDs versus oral NSAIDs†				
Pain:				
Week 1	1	208	-0.38 (-0.66 to -0.10)	—
Week 2	1	208	-0.19 (-0.47 to 0.09)	—
Week 3	2	529	-0.26 (-0.68 to 0.16)	5.83
Week 4	1	208	-0.10 (-0.37 to 0.18)	—
Function:				
Week 1	1	208	-0.32 (-0.60 to -0.04)	—
Week 2	1	208	-0.24 (-0.52 to 0.04)	—
Week 3	2	529	-0.11 (-0.28 to 0.06)	0.71
Week 4	1	208	-0.10 (-0.38 to 0.17)	—

NA=not available.
 *P<0.05.

†Data not available on stiffness.

statistically significant effect size for improvement in stiffness was seen at one week but not at two weeks.

The clinical response rate ratio was statistically significant in the first but not fourth week (bmj.com). No difference was found between topical NSAIDs and oral NSAIDs.

Adverse events and sensitivity analysis

Topical NSAIDs had no more side effects than placebo. Compared with oral NSAIDs, topical NSAIDs had fewer patients with any adverse events, fewer withdrawals due to side effects, and fewer gastrointestinal side effects but statistically more patients with local side effects such as rash, itch, and burning (bmj.com).

Sensitivity analyses showed that although baseline pain score influenced the statistical inference only, the type of topical NSAID produced significantly different effect sizes (table 2).

Discussion

Most randomised controlled trials of treatment for osteoarthritis last only two weeks, and no trials go beyond four weeks. Meta-analysis of these limited data shows that treatment of osteoarthritis with topical NSAIDs is only beneficial in the first two weeks and at one month is comparable to placebo. Our meta-analysis challenges current guidelines from Europe and America that topical NSAIDs are an effective treatment for osteoarthritis of the knee.

This is only the second meta-analysis of topical NSAIDs. The first reported that topical NSAIDs were effective for “chronic” painful conditions, including osteoarthritis, on the basis of data on pain relief at two weeks.⁴ Unlike that study we focused solely on osteoarthritis, included studies published in the interim, examined outcomes of stiffness and function as well as pain, and examined data beyond two weeks of treatment. The effect of topical NSAIDs may depend on time or more likely reflect the type of drug used, as detected by our sensitivity analyses. This seems to be more

Table 2 Sensitivity analysis of effect size (95% confidence interval) for reduction in pain between topical non-steroidal anti-inflammatory drugs (NSAIDs) and placebo, according to quality of studies, site of osteoarthritis, and pain scores at baseline

Variable	Weeks 1 and 2	Weeks 3 and 4
Study design:		
Double blind parallel	0.39 (0.19 to 0.59)*	0.08 (-0.04 to 0.19)
Double blind crossover	0.77 (0.32 to 1.22)*	NA
Withdrawal rate:		
<10%	0.54 (0.27 to 0.82)*	-0.02 (-0.22 to 0.17)
≥10%	0.20 (0.06 to 0.34)*	0.12 (-0.01 to 0.26)
Site of osteoarthritis:		
Hand	0.77 (0.32 to 1.22)*	NA
Knee	0.41 (0.18 to 0.63)*	0.08 (-0.04 to 0.20)
Hand, hip, and knee	0.27 (0.02 to 0.53)*	0.03 (-0.34 to 0.39)
Baseline pain score:		
<50%	0.32 (-0.06 to 0.70)	-0.01 (-0.18 to 0.16)
≥50%	0.44 (0.21 to 0.67)*	0.14 (-0.01 to 0.92)
Topical NSAIDs:		
Salicylate	0.77 (0.32 to 1.22)*	0.03 (-0.34 to 0.39)
Diclofenac	0.68 (0.38 to 0.99)*	NA
Eltenac	0.10 (-0.01 to 0.22)	0.08 (-0.04 to 0.19)
Ibuprofen	0.64 (0.23 to 1.04)*	NA

NA=not available.
*P≤0.05.

What is already known on this topic

Topical non-steroidal anti-inflammatory drugs (NSAIDs) have been used to relieve the pain of osteoarthritis

Current guidelines recommend topical NSAIDs as an effective treatment for osteoarthritis

What this study adds

No evidence supports the long term use of topical NSAIDs in osteoarthritis

Current recommendations for their use in osteoarthritis need to be revised

problematic in the first two weeks, as a statistically significant heterogeneity and different effects of topical NSAIDs were detected. We obtained a statistically significant asymmetrical funnel plot, indicating that negative studies are less likely to be published and that small studies are more likely to produce larger effect sizes. This publication bias may overestimate the benefit of topical NSAIDs.⁶ We therefore draw two important conclusions from the data: firstly, that further well designed, long term studies (months rather than weeks) are required, and, secondly, that the benefit may be drug specific rather than class specific.

Several caveats need to be mentioned. Firstly, language bias cannot be completely avoided because many studies in non-English are not indexed in the databases.⁷ Secondly, results may have been confounded by different numbers of trials being pooled at different time points. Finally, we pooled trials that examined different topical NSAIDs that may have different efficacy. To minimise this bias, we used a sensitivity analysis.

In conclusion, research evidence to support the long term use (more than one month) of topical NSAIDs in osteoarthritis is absent. Current recommendations that support their use in osteoarthritis need to be revised.

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